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Zinc Levels in Serum, Hair, and Atherosclerotic Plaques, and MMP-9/TIMP-1 Concentrations in Carotid Atherosclerosis: Insights from Symptomatic and Asymptomatic Patients

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Abstract This study explored zinc levels in serum, hair, and carotid artery atherosclerotic plaques, along with the concentrations of matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) in serum, in patients with carotid atherosclerosis, comparing asymptomatic individuals with those who had experienced a stroke. In stroke patients, serum TIMP-1 levels were significantly higher than in asymptomatic patients. Furthermore, patients with symptomatic carotid atherosclerosis exhibited lower serum zinc levels and zinc concentrations in atherosclerotic plaques compared to asymptomatic patients, emphasizing the role of zinc in the pathogenesis of carotid atherosclerosis complications. Elevated blood glucose levels were associated with reduced zinc levels in hair, while higher MMP-9 concentrations in serum were correlated with increased zinc levels in serum and a decrease in zinc concentrations in hair.

Keywords Matrix metalloproteinase-9 (MMP-9), Tissue inhibitor of metalloproteinase-1 (TIMP-1), Zinc of the serum, Hair, Atherosclerotic plaques of carotid artery, Carotid atherosclerosis, Stroke

1. Introduction

Coronary artery disease and cerebrovascular disorders are major factors contributing to mortality in several countries. These diseases significantly contribute to the overall mortality rate, accounting for 82.3% in men and 85.8% in women [1]. Atherosclerosis plays a key role in the development of these diseases. Approximately 75% of coronary thrombosis cases leading to myocardial infarction and about 90% of carotid thrombosis cases causing acute cerebrovascular accidents are caused by the instability of atherosclerotic plaques (AP) [2].

Currently, there is no widely accepted method for predicting a stroke before the onset of the first symptoms. In patients with symptomatic carotid artery stenosis, activation of matrix metalloproteinases (MMPs), tissue inhibitor of metalloproteinases (TIMP), and S100B protein may be observed [11].

Zinc (Zn), as an essential trace element for the human body, can significantly influence the development of atherosclerosis. It is involved in various processes related to the risks of atherosclerosis, such as lipid metabolism, glucose metabolism, and blood pressure regulation, performing both positive and negative functions [9]. Numerous studies have shown that zinc deficiency may be associated with risk factors for diabetes and cardiovascular diseases, and that zinc supplementation can have a significant impact on the prevention and treatment of these conditions. Therefore, studying the role of zinc may contribute to the development of new approaches for the prevention and therapy of diabetes and cardiovascular diseases [10]. There is currently sufficient evidence supporting the relationship between zinc levels and atherogenic risk factors; however, the direct interaction between zinc and atherosclerosis remains poorly understood.

The aim of the study is to investigate the zinc levels in serum, hair, and atherosclerotic plaques of the carotid artery, as well as the concentrations of MMP-9 and TIMP-1 in patients with carotid atherosclerosis, comparing asymptomatic individuals with those who have suffered a stroke.

2. Materials and Methods

The study included 148 patients (112 men and 36 women)

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aged 45 to 89 years (mean age 65.35±0.73 years) diagnosed with carotid atherosclerosis, confirmed by color duplex scanning of the extracranial branches of the brachiocephalic arteries. Patients with hemodynamically significant carotid artery stenosis (n=30) were referred for carotid endarterectomy at the Tashkent Medical Academy. These patients were divided into two groups: symptomatic (n=18) and asymptomatic (n=12), based on the presence or absence of a history of acute cerebrovascular accident (CVA) or transient ischemic attack (TIA).

Atherosclerotic plaque samples were obtained immediately after surgery and sent to the laboratory for zinc content analysis. Blood was collected from the antecubital vein the day before surgery in the morning after a 12-hour fast. All venous blood samples were immediately centrifuged, and serum was frozen at -20℃. Serum zinc levels were determined using the "Zinc-Vital" reagent kit (Russia) on a Mindray BS-200 biochemical automatic analyzer (China). Zinc levels in hair and atherosclerotic plaques were measured using inductively coupled plasma optical emission spectrometry on an Optima 2100 DV analyzer (USA). MMP-9 and TIMP-1 concentrations were determined using standard ELISA test kits from Bender-Medsystems GmbH (Austria) on a Plate Reader spectrophotometer from Hospitex Diagnostics (Italy).

Statistical analysis included calculating the mean (M) and standard error (m) for each sample, with results presented as M±m. To identify differences between groups, the Student's t-test was applied at a significance level of $p<0.05$. The correlation between variables was analyzed using Pearson's correlation coefficient.

3. Results and Discussion

Table 1. The clinical and anamnestical characteristics of the patients

Indicators	group 1 (n=12)	group 2 (n=18)
Age, years (M±m)	60,42±1,81	63,44±1,52
Men (n/%)	10 (83)	17 (94)
Women (n/%)	2 (17)	1 (6)
Hypertension (n/%)	10 (83)	17 (94)
Hyperlipidemia (n/%)	6 (50)	11 (61)
Obesity (n/%)	2 (17)	5 (28)
Type 2 Diabetes Mellitus (n/%)	4 (33)	11 (61)
Angina pectoris: (n/%) Functional class II Functional class III	10 (83) 9 (75) 1 (8)	18 (100) 16 (89) 2 (11)
Myocardial infarction in medical history (n/%)	1 (8)	3 (17)
DSCA, % (M±m)	72,67±5,18	76,94±3,30

Note: DSCA – degree of stenosis of the carotid arteries.

When comparing the symptomatic and asymptomatic patient groups, no significant differences were found in age, gender, lipid levels, or the presence of a history of hypertension, ischemic heart disease, myocardial infarction, and type 2 diabetes. However, in symptomatic patients, the glucose level was 1.3 times higher (7.18±0.68 mmol/L) compared to asymptomatic patients (5.70±0.28 mmol/L) ($p=0.05$). The clinical and anamnestical characteristics of the patients are presented in Table 1.

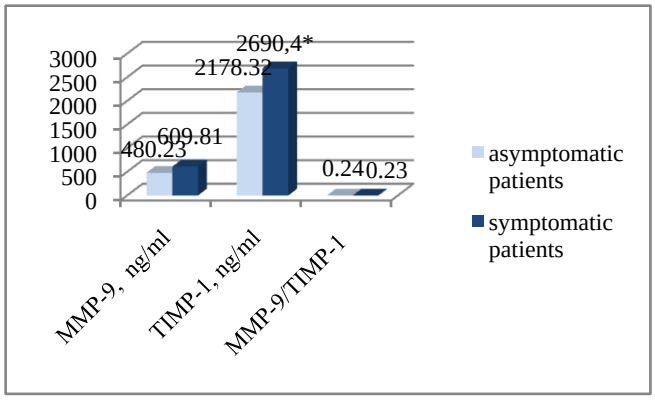
Significant differences were found in the zinc levels in serum and atherosclerotic plaque biopsies of the carotid artery in patients. In symptomatic patients, the serum zinc level was 1.2 times lower (14.59±0.56 μmol/L) compared to asymptomatic individuals (17.68±1.03 μmol/L) ($p=0.014$). The zinc level in atherosclerotic plaques was also 2.4 times lower in the symptomatic group (51.76±8.64 μg/g) compared to asymptomatic patients (126.66±33.95 μg/g) ($p=0.041$). As for the zinc level in hair, it was 183.78±17.03 μg/g in the asymptomatic group and 224.84±24.12 μg/g in the symptomatic group, with the difference being statistically insignificant ($p=0.18$) (Table 2).

Table 2. Zinc (Zn) concentration in different biological materials in patients with symptomatic and asymptomatic carotid atherosclerosis

Biological Material	group 1 (asymptomatic)	group 2 (with symptomatic)
Zn in serum, μmol/L	17,68±1,03	14,59±0,56*
Zn in hair, μg/g	183,78±17,03	224,84±24,12
Zn in atherosclerotic plaques (AP), μg/g	126,66±33,95	51,76±8,64*

Note: * - $p<0,05$.

When comparing the groups by MMP-9 and TIMP-1 levels in serum and the MMP-9/TIMP-1 ratio, the TIMP-1 concentration in serum was 1.2 times higher in the second group of symptomatic patients (2690.40±166.01 ng/mL) compared to the first group (2178.32±166.73 ng/mL) ($p=0.038$) (Fig. 1).



Note: * - $p<0,05$.

Figure 1. Concentrations of MMP-9, TIMP-1, and the MMP-9/TIMP-1 ratio in serum in groups of patients with symptomatic and asymptomatic carotid atherosclerosis

Correlation analysis in the asymptomatic patient group revealed a significant inverse correlation between serum glucose concentration and zinc levels in hair (r=-0.65;

$p<0.01$). A trend towards a weak inverse correlation between serum and hair zinc levels was also observed ($r=-0.39$; $p<0.1$). Furthermore, a strong positive correlation was found between MMP-9 levels and serum zinc concentration ($r=0.78$; $p<0.0001$), as well as a noticeable inverse correlation with zinc levels in hair ($r=-0.66$; $p<0.01$).

The question of the feasibility of performing carotid endarterectomy for any degree of carotid stenosis and the presence of ultrasound signs of "unstable" atherosclerotic plaque structure is currently actively discussed, both in patients with a history of acute cerebrovascular accident and in those with asymptomatic atherosclerosis [4]. In this regard, randomized controlled trials evaluating specific panels of vascular biomarkers are of particular importance. This will allow for the timely identification of patients with vulnerable atherosclerotic plaques, and thus, with a high risk of cardiovascular complications. In turn, this will simplify and improve the decision-making process regarding surgical intervention and pharmacological treatment strategies.

In our study, serum zinc levels were lower in patients with ischemic stroke compared to asymptomatic patients, which is consistent with the results of other researchers [6].

Studies on the relationship between dietary zinc intake and stroke have shown that this trace element may act as a protective factor against stroke. Increased zinc intake may help prevent or alleviate stroke symptoms, as well as mitigate the manifestations of related diseases [5].

The inverse relationship between zinc levels in serum and hair can be explained by the opposing effects of intracellular and extracellular zinc. Intracellular zinc promotes an increase in calcium levels inside the cell through various mechanisms, highlighting its role in heart failure and hypertension. At the same time, extracellular zinc exerts an opposite effect by blocking calcium channels, which explains the decrease in its concentration in serum despite the increased zinc levels in cardiomyocytes and erythrocytes in patients with hypertension. These findings from the literature confirm that zinc plays a key role in the normal functioning of the cardiovascular system as well as in its diseases. However, the relationship between zinc and cardiovascular disorders is so complex that its final explanation remains unclear [7].

According to Mengjia Pu et al., an increase in TIMP-1 levels may be associated with cognitive impairments following a stroke [8]. The results of other studies have also shown that patients with simultaneously higher levels of TIMP-1 and MMP-9 had the highest risk of cognitive impairments. Higher serum TIMP-1 levels were associated with an increased risk of cognitive impairments following acute ischemic stroke, regardless of the presence of risk factors [3]. According to the findings of Zielińska-Turek Justyna et al., elevated levels of MMP-9 and TIMP-1 in patients with ischemic stroke compared to patients with asymptomatic carotid artery stenosis after endarterectomy indicated that these biomarkers could be good predictors of ischemic stroke in patients who have undergone carotid endarterectomy [11].

4. Conclusions

1. In patients with carotid atherosclerosis and a history of acute cerebrovascular accident (CVA) or transient ischemic attack (TIA), serum zinc levels and zinc levels in atherosclerotic plaques are lower compared to asymptomatic patients. This confirms the significant role of zinc levels in biological samples in the pathogenesis of carotid atherosclerosis complications.
2. Increased blood glucose concentration is accompanied by a decrease in zinc levels in hair.
3. As the MMP-9 level in the blood increases, the zinc concentration in serum increases, while it decreases in hair.
4. In patients who have suffered a stroke or TIA, the TIMP-1 concentration in serum is higher compared to asymptomatic patients.

Conflict of Interests

The authors declare absence of conflict of interests.

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